

REMARKS

The applicant expresses appreciation to the Examiner for consideration of the subject patent application. This amendment is in response to the Office Action mailed May 7, 2003. Claims 1-13 were rejected.

Claims 1-36 were originally presented. Claims 1-13 remain in the application. Claims 14-36 have been canceled and withdrawn from consideration. Claim 1 has been amended. The support of the amendment can be found throughout the application.

Claim Rejections - 35 U.S.C. § 103

Claims 1-10 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Cha et al. (5,702,717) in view of EP 0092918(Churchill).

The burden is on the Examiner to establish a case of *prima facie* obviousness. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In order to do this by combining references, the prior art must provide some reason or motivation to make the claimed compositions, *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc). When making a rejection under 35 U.S.C. § 103 there are three fundamental areas the Examiner is required, under 37 C.F.R. § 1.106 and MPEP § 706.02, to cover. First, the rejection should set forth the differences between the claims and the prior art. Second, the proposed modification of the applied references necessary to arrive at the claimed subject matter should be clearly stated. Third, there must be an explanation as to why such proposed modifications would be obvious.

In the rejections entered by the Examiner under § 103, there is a common flaw which cannot be resolved simply by the Examiner making an allegation that "it would be obvious". There must be some reason, suggestion or motivation in the art cited to combine the references in the manner stated by the Examiner. Were it not for first having read the Applicants' disclosure and then by hindsight application attempting to piece together portions of each reference rather than considering each reference for what it teaches as a whole, it is not believed a rejection would have been entered. With the above background in mind the rejection under 35 U.S.C. § 103 will be discussed.

The present invention provides drug delivery systems that are biodegradable, exhibit improved reverse thermal gelation behavior, and provide improved drug release characteristics. The drug delivery systems of the present invention are biodegradable polymeric systems possessing reverse thermal gelation properties comprising a mixture of at least a Component I triblock copolymer and a Component II triblock copolymer. The triblock copolymers of the present invention comprise biodegradable polyester A-polymer blocks and polyethylene glycol B-polymer blocks, wherein the B-polymer block of said Component I triblock copolymer has an average molecular weight of 900 to 2000 Daltons and the B-polymer block of said Component II triblock copolymer has an average molecular weight of 600 to 2000 Daltons. The Component I triblock copolymer has an average molecular weight of between 2500 to 8000 Daltons and the component II triblock copolymer has an average molecular weight of between 800-7200 Daltons. The biodegradable polymeric system of the present invention is water soluble and contains 51 to 83 % by weight of hydrophobic A polymer blocks and 17 to 49 % by weight of hydrophilic B polymer blocks.

In Cha, the block copolymer contains less than 50% by weight of a hydrophobic A polymer block and more than 50% by weight of a hydrophilic B polymer block(PEG)(Claim 1). Also in col.8, lines 32-35, Cha discloses that “biodegradable block copolymer possessing thermally reversible gelation properties are prepared wherein the hydrophilic B block makes up about 50-85% by weight of the copolymer and the hydrophobic A block makes up about 15 to 50% by weight of the copolymer.” In contrast, the biodegradable polymeric system of the present invention comprises 51 to 83% by weight of a hydrophobic A polymer block and 17 to 49 % by weight of a hydrophilic B polymer block(PEG)(amended Claim 1).

This disclosure by Cha is in conformity with what is commonly known by those skilled in the art regarding solubility of triblock polymers. Specifically, it is generally taught that any polymer having a hydrophobic content in excess of 50% by weight is substantially insoluble in water and can only be made appreciably soluble in aqueous systems, if at all, when a certain amount of an organic cosolvent has been added.

Conversely, the present invention is based on the discovery that a **mixture** of block copolymers, where the A-blocks are a relatively hydrophobic and the B-block is a relatively

hydrophilic polyethylene glycol (PEG), having a hydrophobic content of between about 51 - 83% by weight exhibit water solubility at low temperatures and undergo reversible thermal gelation at mammalian physiological body temperatures. With such high hydrophobic contents (51 - 83%), it is unexpected that such block copolymers would be water soluble.

Furthermore, it was an unexpected discovery that a **mixture** of block copolymers with such a large proportion of hydrophobic component would be water soluble below normal room temperature such as refrigerator temperatures (5°C). In addition, despite the fact that hydrophobic polymer block(s) are the major component (51- 83%), the water soluble mixture of block copolymers of the present invention aid in an additional increase in drug solubility when combined in an aqueous phase of the block copolymers. Finally, as the Examiner acknowledges, Cha does not teach “a mixture of two different copolymers.”

Churchill discloses amphipathic copolymers which are capable of absorbing water to form a hydrogel when placed in water or an aqueous physiological-type environment in an animal body. Churchill does not teach a block copolymer system having reverse thermal gelation properties. In addition, it was not known in the art prior to the present invention that using a higher hydrophobic polymer content for the A-blocks would result in a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures. In fact, both of these properties are counterintuitive. Using more of a hydrophobic polymer block provides a triblock polymer that is unexpectedly water soluble.

Furthermore, it was unexpected to find that these ABA-block tripolymers would gel at higher temperatures and exist in a liquid state at lower temperatures. There is no indication that the Churchill block copolymers are soluble in aqueous solutions at any temperature without the use of organic solvents, nor is there any indication that these drug/polymers can be administered as a solution. Although Churchill discloses blending different copolymers to obtain various release rates duration of release, no motivation is provided to blend various block copolymers to obtain a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures, as claimed in the present invention.

In summary, first, nothing in Cha or Churchill suggests a block copolymer having less than 50% of a hydrophilic component. The present invention requires less than 50%

hydrophilic content, whereas, the cited reference requires greater than 50% of a hydrophilic component. Second, the reverse thermal gelation properties discussed previously are not present in the Churchill disclosure and are not realized by the Churchill. Furthermore, the presently claimed block copolymer has a reversal thermal gelation temperature lower than the block copolymers disclosed in Cha due to different ratios of hydrophobic and hydrophilic blocks within the block copolymer mixture. Third, the fact that the present invention includes more of the hydrophobic component, and yet, the mixture is water soluble is certainly unexpected. Furthermore, no motivation is provided to combine Churchill, which teaches blending copolymers to regulate the release rate and duration, with Cha to obtain a system with improved reverse thermal gelation properties as claimed in the present invention. Finally, even combining the cited references still does not teach or suggest all of the elements of the amended claim 1. Since claims 1-10 and 13 are dependent claims based on claim 1, they are patentable if claim 1 is patentable based on the above reasons.

Therefore, in view of the above, it is believed that the Examiner has failed to establish a case of *prima facie* obviousness. In other words, one of ordinary skill in the art when combining all the knowledge and methods disclosed in the cited prior art, at the time of the invention was made, would not come up with the triblock copolymer mixtures as claimed in the present invention. Thus, the Examiner is respectfully requested to withdraw the rejections of Claims 1-10 and 13 as being unpatentable over the cited references.

Claims 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Cha et al. (5,702,717) in view of EP 0092918(Churchill) in further view of Youxin et al(Journal of Controlled Release (32)1994 121-128)(hereafter as "Youxin").

First, since claims 11-12 are dependent claims based on claim 1, they are patentable if claim 1 is patentable based on the above reasons. Furthermore, Youxin does not teach a block copolymer system having reverse thermal gelation properties. There is no indication that the Youxin block copolymers are soluble in aqueous solutions at any temperature without the use of organic solvents, nor is there any indication that these drug/polymers can be administered as a solution. Although Youxin discloses depending on the PEO content and lactyl/glycol ratio, degradation rates can be adjusted, no motivation is provided to blend various block copolymers

to obtain a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures, as claimed in the present invention. Therefore, that the Examiner has failed to established a case of *prima facie* obviousness. The examiner is respectfully requested to withdraw the rejections of Claims 11-12 as being unpatentable over the cited references.

CONCLUSION

In light of the above, Applicant respectfully submits that pending claims 1-13 are now in condition for allowance. Therefore, Applicant requests that the rejections and objections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is strongly encouraged to call undersigned at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 23rd day of July, 2003.

Respectfully submitted,



M. Wayne Western
Registration No. 22,788

THORPE NORTH & WESTERN, LLP
P.O. Box 1219
Sandy, Utah 84091-1219
Telephone: (801) 566-6633